

Adrenalectomy for Control of Cancer of the Breast

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A TEAM OF SPECIALISTS composed of two surgeons, an endocrinologist, a therapeutic radiologist and a pathologist have been working together at the Cedars of Lebanon Hospital in Los Angeles for the purpose of treating a group of patients with advanced metastatic cancer of the breast. The treatment consists of the surgical removal of the ovaries and the adrenal glands.

This cooperative therapeutic endeavor was stimulated by the reports of Huggins^{4,5} who first introduced this form of treatment. Subsequent published reports by other groups also noted that favorable palliative results could be obtained in some of the patients subjected to total adrenalectomy.^{3,6-10,13-15}

This report summarizes the experience with, and program of management of, ten patients with advanced metastatic cancer of the breast treated by bilateral oophorectomy and adrenalectomy and who have now been observed for one year or longer.

CONDITION OF PATIENTS

Combined oophorectomy and adrenalectomy was performed in ten patients with metastatic carcinoma of the breast. All had metastasis to soft tissue and/or bone of significant clinical degree associated with active progressive symptoms due to the metastatic lesions. In every case, the metastatic lesions could be objectively demonstrated. There was no selection as to age, pathological type of tumor, type of metastasis or previous therapy. Eight of the ten patients had had varying amounts of hormonal and x-ray therapy previously, despite which the disease was still progressing. None of the patients had had surgical oophorectomy. Two of the patients had no previous palliative therapy for the metastatic disease.

PREOPERATIVE MANAGEMENT

1. Preoperative Studies

(a) *Routine tests normally obtained before any type of elective surgical procedure.* These tests in-

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• Bilateral oophorectomy and adrenalectomy were used in the treatment of ten patients with advanced metastatic carcinoma of the breast, and particular attention was given to preoperative and postoperative management by a team of specialists including surgeons, endocrinologist, radiologist and pathologist.

Objective and gratifying clinical remissions were achieved in three of the ten patients in this series following total oophorectomy and adrenalectomy. The remaining seven patients all subsequently died of metastatic disease. There were no operative deaths.

Known cerebral or hepatic metastasis contraindicates adrenalectomy for metastatic cancer of the breast. Five of the seven patients not benefited by the operation had either cerebral or hepatic metastasis.

The best candidates for adrenalectomy are premenopausal women who have previously had a clinical remission following oophorectomy and who have subsequently relapsed.

The indications for adrenalectomy in the postmenopausal woman are not clear.

clude urinalysis, complete blood cell count, platelet count, blood typing and serum creatinine determination. In the event of known or suspected cardiovascular disease, an electrocardiograph and a 6-foot film of the chest for heart size were also obtained.

(b) *Serum electrolytes.* Serum sodium, potassium, chloride and carbon dioxide combining power determinations were done. These served as a baseline for postoperative serum electrolyte determinations, helpful in adjusting postoperative adrenal replacement therapy.

(c) *Tests of calcium metabolism* (particularly in patients with osseous metastasis). These studies served as preoperative baseline values for subsequent postoperative determinations. These tests are an aid in the evaluation of the growth activity of osseous metastasis before and after adrenalectomy.^{7,8}

(1) Serum calcium.

(2) Serum phosphorus.

(3) Serum alkaline phosphatase.

(4) Quantitative 24-hour urine excretion of calcium on the third day of a low calcium (100 mg.) diet.

(d) *Hormonal studies.* The only hormonal study

done routinely was determination of the 24-hour urine excretion of *total estrogens*. This was repeated two or three months after operation to determine the effect of adrenalectomy on estrogen production.¹ Preoperative tests of adrenal cortical function were not routinely done because it was felt they did not contribute to the practical management of the patients. All patients were routinely protected against operative and postoperative adrenal insufficiency by a standard schedule of adrenal cortical replacement therapy.

(e) *X-ray studies*. Bone surveys and films of the chest for the detection of metastatic lesions were obtained.

2. Preoperative Adrenal Cortical Preparation

Nine of the ten patients had two-stage adrenalectomy. Adrenal cortical replacement therapy was done routinely before the first stage of the adrenalectomy. This was done for the following reasons: (1) What the functional capacity of the remaining adrenal gland will be after unilateral adrenalectomy cannot be forecast accurately before operation; (2) The adrenal glands of patients with advanced carcinoma may already be subjected to stress prior to operation;¹⁸ (3) Unsuspected metastatic carcinoma in the adrenal glands was discovered in a high proportion of the patients in this series.

Because of these factors, it was felt that it is easier and safer to protect the patient against possible operative or postoperative adrenal cortical insufficiency than to treat adrenal collapse when it occurs.

The following treatment schedule was followed:

Cortisone acetate: Two days before operation—50 mg. intramuscularly every 12 hours. One day before operation—50 mg. intramuscularly four times a day. Two hours before operation—150 mg. intramuscularly.

(Note: Desoxycorticosterone acetate (DOCA) and sodium chloride were used preoperatively in only two cases, early in the series. In those two cases these agents were used as recommended by Huggins and postoperative peripheral and pulmonary edema was a problem. In the subsequent patients these substances were not given and this complication did not occur.)

SURGICAL TECHNIQUE

In all but one case in this series the operation was done in two stages: Bilateral oophorectomy and left adrenalectomy in the first stage, and right adrenalectomy a week or ten days later. In one instance the entire procedure was done in one stage. It is felt that when the patient is in reasonably good condition the one-stage procedure can be done safely.

Oophorectomy is done through a suprapubic midline incision. The patient is then placed on her right side in a "kidney position," and the left adrenal gland is removed through an incision going through the bed of the 12th rib. The lumbar muscles are divided in the line of the incision, Gerota's fascia is incised, the kidney is drawn downward and the adrenal gland exposed. Because the gland is extremely friable, clamps should be applied to surrounding adventitious tissue rather than to the gland itself in providing traction for exposing the adrenal artery and veins. On the right side the upper pole of the gland must be separated from the posterior surface of the liver, and the deep surface must be carefully dissected from the vena cava.

OPERATIVE MANAGEMENT

The preoperative preparation with cortisone given intramuscularly was frequently sufficient to carry the patient through the surgical procedures without incident or need of further steroid therapy. However, the following materials* were always on hand in the operating room in case of sudden need: (1) Hydrocortisone for intravenous use, (2) aqueous adrenal cortical extract, and (3) levarterenol bitartrate (Levophed®). The intravenous hydrocortisone was always set up and ready for infusion in the event of the following indications: (1) Significant persistent decrease in blood pressure, and (2) a pulse rate of 120 or more. It was found necessary to supplement the cortisone maintenance of the patient with intravenous hydrocortisone in about one-third of the cases. Aqueous adrenal cortical extract was used in two patients because of a precipitous drop in blood pressure and it restored the pressure to normal levels while the drip of intravenous hydrocortisone was being started. In the series no occasion arose for the use of Levophed.

POSTOPERATIVE MANAGEMENT

The following regimen was the basic postoperative routine (modified, of course, to suit each patient's individual requirements and problems):

Day of operation: Cortisone acetate, 50 mg. intramuscularly every 4 to 6 hours. 1,500 cc. of 5 per cent glucose in distilled water intravenously. Fluids by mouth as tolerated.

First postoperative day: Cortisone acetate, 50 mg. intramuscularly every 6 hours. 1,000 cc. of 5 per cent glucose in distilled water intravenously. Fluids by mouth and soft diet as tolerated.

Second postoperative day: Cortisone acetate, 50

* Merck & Co. supplied a saline suspension of cortisone acetate for intramuscular use and infusion concentrate of hydrocortisone for intravenous administration; and Parke, Davis & Co. supplied aqueous adrenal cortical extract (Eschatin).

TABLE 1.—Results of Bilateral Oophorectomy and Adrenalectomy for Metastatic Carcinoma of the Breast

Patient	Age	Time of Radical Mastectomy Before Adrenalectomy	Time of Appearance of Distant Metastasis Before Adrenalectomy	Hepatic or Cerebral Metastasis	Previous Treatment	Response to Adrenalectomy		Final Status 1 Year After Adrenalectomy
						Objective	Subjective	
1.	36	4 years	2½ year S 16 months B	+ C	XR 1950 Cast XR 1953 Testost. 1953	0	+ for 5 mos.	Died 7 months postoperatively
2.	49	3 years	3 months S	0	0	+	+	Still in remission 12 months postoperatively
3.	41	4 years	2 months S	0	PO XR	+	+	Still in remission 12 months postoperatively
4.	39	1 year	2 months S B	+ H	PO XR Cast XR Testost.	0	0	Died 10 months postoperatively
5.	47	5 years	2 years S B	0	Cast XR Testost. Cr PO ₄	+	+	Still in remission 12 months postoperatively
6.	40	5 years	2 years S	+ C	Cast XR PO XR Testost.	0	0	Died 6 weeks post-operatively of cerebral metastasis
7.	56	5 years	3 years S B	0	XR Testost. XR PO	0	+ for 4 mos.	Died 11 months postoperatively
8.	48	4 years	2 years S	+ C	Estrogens XR Cortisone	0	0	Died 6 weeks post-operatively of cerebral metastasis
9.	73	2 years	2 months S	0	Cr PO ₄	0	0	Died 3 months postoperatively
10.	49	3 years	1 year B S	+ H	XR PO XR Testost.	+ for 5 mos.	+ for 5 mos.	Died 7 months postoperatively

Legend: S—Soft tissue metastasis.
B—Bone metastasis.
C—Cerebral metastasis.
H—Hepatic metastasis.

XR—Radiation therapy.
PO XR—Postoperative radiation therapy.
Cast XR—Castration by radiation therapy.
Cr PO₄—Intraleural radioactive chromic phosphate therapy.

mg. intramuscularly every 8 hours. Soft diet and fluids by mouth as tolerated. No parenteral fluids unless oral intake inadequate.

Third postoperative day: Cortisone acetate, 50 mg. intramuscularly every 12 hours.

Fourth postoperative day: Cortisone acetate, 37.5 mg. intramuscularly every 12 hours.

Fifth postoperative day: (1) If the patient has had only a first stage adrenalectomy and is to be prepared for removal of the second adrenal gland, the preoperative hormonal preparation is exactly as outlined above under *Preoperative Management*, beginning on this day. (2) If the patient has had bilateral adrenalectomy in one stage or a second stage adrenalectomy, administration of cortisone by mouth is begun on this day. The dose is 12.5 mg. four times a day. The patient is maintained on this dose until discharge from the hospital.

The Use of DOCA and Sodium Chloride

The need for supplementary *sodium chloride* is gauged by such factors as daily serum electrolyte

determinations, urinary output, presence or absence of edema, and the age and cardiac status of the patient. The daily dose of sodium chloride given varies from 1 to 4 gm., preferably by oral administration. If parenteral salt is needed during the first or second postoperative day, it is given in the form of 0.45 per cent normal saline solution.

DOCA was not given in this series until the maintenance oral dose of cortisone was begun on the fifth postoperative day or later. Usually at this time DOCA was given sublingually, 2 mg. daily.

Maintenance Hormonal Management After Discharge from the Hospital

All of the patients were satisfactorily maintained on cortisone, 50 mg. daily by mouth, given in divided doses, and sublingual DOCA, 2 mg. daily. Most patients did not require supplemental doses of sodium chloride but a few were given 2 to 4 gm. of salt per day. All the patients were instructed to notify the endocrinologist of the group immediately if they had a respiratory tract infection or febrile

RESULTS

1. Operative Mortality and Morbidity

Nineteen operations were done on ten patients. There were no operative or postoperative deaths. There were two postoperative complications. In one patient, the oldest in the series, a 73-year-old woman, bilateral wound infection developed in the adrenalectomy incisions. The other complication, in another patient, was slight pneumothorax due to a pleural tear with an estimated 10 per cent collapse of the lung on the involved side.

2. Subsequent Clinical Results

One year after operation three of the ten patients remained in complete objective and subjective remission and seven had died of metastatic disease. The salient data concerning these patients are summarized in Table 1.

The following summaries illustrate the clinical course of the three patients who had excellent remission following combined oophorectomy and adrenalectomy.

CASE 1. A 49-year-old white woman had a right-radical mastectomy for carcinoma of the breast in July 1951. She was well until March 1954 when progressive shortness of breath developed due to bilateral pleural effusions. She required thoracentesis four times prior to adrenalectomy. Pathological examination of the pleural fluid showed the presence of carcinoma cells. X-ray studies showed a massive pleural effusion on the right with a small amount of fluid in the left pleural cavity (Figure 1). A bone survey showed no abnormality. Bilateral oophorectomy and adrenalectomy was done in July 1954. Following operation there was a prompt disappearance of the pleural effusions. The patient returned to full activity and at last report was managing her business without assistance. She said she felt "wonderful." An x-ray film of the chest in April 1955 was normal except for evidence of thickening of the basal pleura on the right (Figure 2).

CASE 2. A 41-year-old white woman had a right radical mastectomy for carcinoma of the breast in December 1950. She was well until April 1954 when aching pains developed in the left shoulder and chest, and shortness of breath was noticed. Examination revealed a bilateral pleural effusion and a metastatic right supraclavicular lymph node. No abnormality was seen in an x-ray study of the bones. The metastatic lymph node was removed and pathological examination revealed carcinoma. Pathological examination of pleural fluid also revealed the presence of carcinoma cells. Bilateral oophorectomy and adrenalectomy was performed in June 1954. There was prompt disappearance of the pleural effusions and pulmonary nodules. In December 1954 a recurrence of right pleural effusion developed. A single treatment with the pleural instilla-

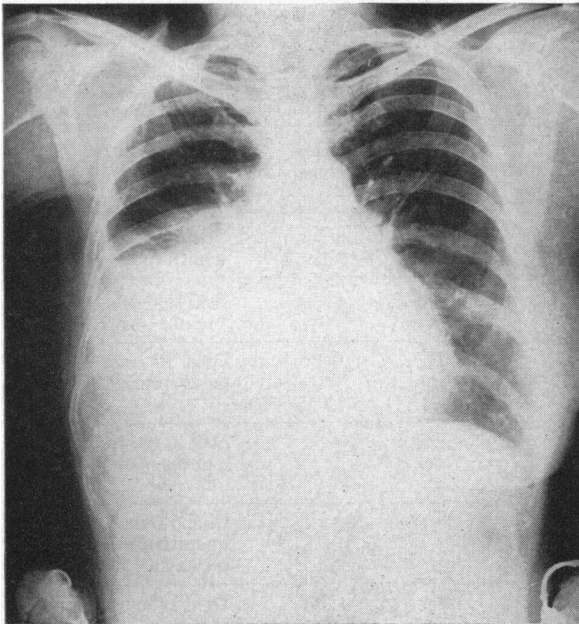


Figure 1.—Preoperative x-ray film of chest (Case 1). Note large pleural effusion on the right.

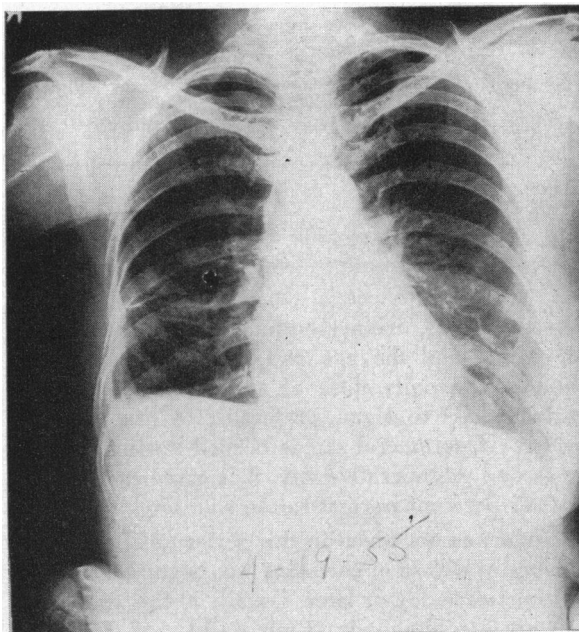


Figure 2.—X-ray film of chest (Case 1) nine months after bilateral oophorectomy and adrenalectomy. Note resolution of right pleural effusion. Only thickening of the basal pleura on the right remains.

illness of any sort, any injuries, any contemplated major or minor surgical procedure, or such symptoms as malaise, anorexia and nausea. This was for the purpose of possible immediate adjustment of replacement hormonal therapy to avoid acute adrenal insufficiency secondary to stress.

tion of radioactive chromic phosphate resulted in prompt clearing of the effusion. The patient was well and free of any objective metastatic disease 13 months after operation. An x-ray film of the chest in June 1955 was normal except for some thickening of the right pleura at the costophrenic angle.

CASE 3. A 47-year-old white woman had a right radical mastectomy in 1949. She received postoperative x-ray therapy because of metastasis to the axillary lymph nodes. In February 1952 bilateral pleural effusions developed. At this time treatment consisted of irradiation of the ovaries, bilateral intrapleural instillation of radioactive chromic phosphate, and the intramuscular administration of testosterone. These measures resulted in improvement in the pulmonary metastatic disease. However, progressive metastatic involvement of the bones developed, with generalized pain, malaise, fatigue and semi-invalidism. X-ray studies in July 1954 showed multiple osteoblastic metastasis involving the entire spine, pelvis, upper femurs, skull and ribs. Bilateral oophorectomy and adrenalectomy were performed in July 1954. The patient returned to full activity, had no pain or symptoms of any kind and "feels wonderful." She was clinically well 12 months after operation.

3. Comments on Treatment Failures

When this study was begun the authors did not realize the hopeless prognosis for patients with hepatic or cerebral metastasis regardless of the mode of treatment. Five of the seven patients in this series in whom treatment failed had either hepatic or cerebral metastasis. Three of these patients had cerebral metastasis, and in only one of the three cases was this fact known prior to the combined operative procedure. The cerebral involvement in the other two patients did not become apparent until, after operation, it was manifest by the clinical development and progression of neurological signs and symptoms. The two patients with hepatic metastasis were found to have liver involvement at the time of laparotomy for oophorectomy.

In most instances the ultimate response of the disease to the operation was apparent by the time the patient left the hospital. At this time the patients were receiving adrenal replacement maintenance doses of cortisone and DOCA and the temporary beneficial effects of large doses of cortisone had ended. Those who were to benefit by the operation felt well on maintenance doses of cortisone and as time went on continued to feel better and better. On the other hand, those who did not benefit from the operation did not feel well on maintenance adrenal replacement medication, and adjustments in adrenal replacement medications did not help. However, two of the seven patients in whom the treatment was a failure had temporary periods of im-

provement before relapsing and eventually dying of the disease. One of these patients had an impressive subjective response for a period of four months after operation, during which time she felt very well despite the objective evidence of spread of the disease. The case history is as follows:

A 56-year-old white woman had right radical mastectomy in 1949. Early in 1952 a sternal mass first appeared. Despite an intensive course of irradiation and a full course of testosterone therapy there was no regression in the sternal mass. Moreover, metastatic involvement of the sternum and the lungs became evident. Consequently bilateral total oophorectomy and adrenalectomy was performed and completed in August 1954. Following the operation the patient subjectively felt well and stated she felt wonderful. She had no pain or distress of any kind, had a hearty appetite and was able to perform all of her customary duties. She felt so well she was able to take a trip by herself to the East Coast to see her family for a period of five weeks. There were, however, no objective changes in the sternal mass or in the x-ray appearance of the metastatic lesions in the sternum and the lungs. The subjective sense of well-being ended approximately four months postoperatively when the patient began to complain of pain across the chest, cough, weakness and malaise. At this point a course of cobalt treatments was directed at the sternal mass, which definitely flattened and seemed to melt away. However, the pulmonary metastatic lesions were increasing in size and number despite the cobalt therapy. Subsequently the patient developed progressive shortness of breath due to rapidly progressive metastatic disease of the lungs, and 11 months after operation she died of metastatic pulmonary disease.

This patient differed from all the other patients who were unresponsive to operation in that she felt subjectively very well postoperatively on just maintenance doses of cortisone.

One patient had a partial response to operation, as objectively viewed, for a period of four months:

A 49-year-old white woman had a right radical mastectomy in 1951. In 1953 pain in the back due to vertebral metastasis developed. At this time treatment consisted of x-ray castration, radioactive phosphorus and a full course of testosterone therapy. Despite this therapy the patient ultimately developed massive bilateral pleural effusions which were recurrent and required thoracentesis several times. Because of this, bilateral oophorectomy and adrenalectomy were done in November 1954. During the laparotomy for oophorectomy a large metastatic nodule was found in the right lobe of the liver. Following operation the pleural effusions did not recur and the patient subjectively felt much improved. However, she continued to have intermittent nausea, abdominal bloating and weakness. Four months after operation, generalized aches and pains, anorexia, nausea, abdominal bloating and intense weak-

ness developed. At this time enlargement of the liver was noted. A bone survey showed radiological evidence of progressive bone metastasis. The patient eventually died of hepatic metastatic disease seven months after operation.

This case illustrates the following points:

1. The improvement of metastatic disease in one area (lungs) with the simultaneous progression of metastatic disease in other areas (liver and bones).

2. The very poor prognosis of patients with known hepatic metastasis. In retrospect, any patient such as this in whom liver metastasis is found at the time of oophorectomy would not have been subjected to adrenalectomy.

4. Change of Radiosensitivity After Adrenalectomy

It was observed clinically that three of the patients showed an unusually rapid response to external radiation following bilateral adrenalectomy and oophorectomy. This was particularly true of soft tissue metastatic lesions. Endocrine influence on radiosensitivity has been observed by other investigators in experimental animals. According to a report by Ellinger,² adrenalectomy increases the sensitivity of the animal to total-body irradiation, an effect which is reversed by administration of whole extract of the adrenal cortex or of desoxycorticosterone acetate. Cortisone also makes mice more susceptible to total-body radiation and accentuates the mortality from bacterial and viral infections in irradiated animals. This effect is thought to be related to the action of cortisone on lymphatic tissues. Hypophysectomy also makes the animal more susceptible to total-body irradiation, probably because of the effect of this operation upon the adrenal cortex.

DISCUSSION

Upon review of the cumulative experience of the authors and of others who have reported on use of the operation, it is felt that the following statements are warranted:

1. Bilateral oophorectomy and adrenalectomy is a safe surgical procedure with a low operative mortality, especially if performed by an experienced team.

2. Some patients with progressive metastatic malignant disease of the breast are dramatically and objectively benefited.

3. Known cerebral or hepatic metastasis contraindicates adrenalectomy for therapeutic purposes.

The principal problem and the great unknown about this procedure is how to select patients who will be benefited by the operation. So gratifying were the results in three patients in the present series that the authors are convinced this surgical procedure

has a definite place in the therapeutic choices offered to patients with metastatic malignant breast disease. What, then, are the criteria for advising adrenalectomy in a given patient?

First of all it is well to consider some *don'ts*. This procedure must not be contemplated until the patient has clinically significant metastatic disease—that is, definite symptoms, such as persistent bone pains, malaise, weakness, pleural effusion or extensive local growth. It would be unwise, it is felt, to treat relatively localized, slow-growing, silent metastatic lesions by a drastic procedure such as this. (Experience with adrenalectomy in three patients with early localized silent metastasis, performed subsequent to the presentation of this report, was not good.) Secondly, as already indicated, the known presence of cerebral or hepatic metastasis should discourage the consideration of this operation. As a matter of fact, if liver metastasis is found at laparotomy for oophorectomy, it is the authors' present practice just to perform the oophorectomy and cancel the adrenalectomy. Thirdly, the experience with adrenalectomy in elderly patients was not very satisfactory. Patients in their late sixties or seventies do not seem to tolerate the state of surgically induced adrenal insufficiency as well as younger patients, despite seemingly adequate adrenal replacement therapy. These older patients do not feel as well after adrenalectomy as they did before the operation.

What patients, then, are deemed suitable for total adrenalectomy? With the above contraindications and qualifications in mind, the authors have more or less followed the outline suggested by Pearson and co-workers^{11,12} at the Memorial Center for Cancer and Allied Diseases in New York. In brief, the authors' program of management of patients with metastatic carcinoma of the breast is as follows:

A. Premenopausal Women

1. *Surgical oophorectomy.* This is the first step and the procedure of choice in these patients. It will induce objective and subjective remission in approximately 50 per cent of patients so treated.

2. For patients who had a definite remission with oophorectomy and then had relapse, either a course of androgens or adrenalectomy may be considered. If one wishes to be conservative, a course of androgens may be tried for two or three months and if no definite benefits are achieved thereby, total adrenalectomy should be considered as the next step. In the event of a further remission induced by androgens alone, adrenalectomy may be withheld until relapse occurs. From the available evidence, it would be impossible at this time to state categorically whether androgens or adrenalectomy should be tried first.

3. Patients who have had oophorectomy without definite improvement or remission are not candidates for total adrenalectomy.

B. Postmenopausal Women

The precise indications for total oophorectomy and adrenalectomy are not as clear in this group of patients as in the premenopausal patients. There are those who advocate immediate total oophorectomy and adrenalectomy as the treatment of choice in the event of significant metastatic disease in this group of women. Again, if one wishes to be conservative, a course of estrogens or possibly androgens may be tried before adrenalectomy is considered. It would appear that the decision for or against adrenalectomy in this group of patients is a matter of judgment in which various factors are taken into consideration. The factors to be considered would be the length of time since the primary or original mastectomy, the apparent rate of growth of the metastatic disease, and the response to previous therapy (radiation, estrogens and androgens).

It should be emphasized that, whenever feasible, relatively localized metastatic lesions should be treated by radiation or surgical excision before any systemic modes of therapy are considered.

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ADDENDUM

Since this report was first presented, the authors have performed total oophorectomy and adrenalectomy in five additional patients without surgical mortality. Further experience has in no way altered the opinions and conclusions reported in this paper, but has only served to strengthen the previous observations.

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